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## Evidence-based Series #1-24: Section 1

# The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/*neu*-overexpressing Breast Cancer: A Clinical Practice Guideline

*M. Trudeau, Y. Madarnas, D. McCready, K. I. Pritchard, H. Messersmith,  
and the Breast Cancer Disease Site Group*

A Quality Initiative of the  
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The full Evidence-based Series #1-24 is comprised of 3 sections  
and is available on the CCO website (<http://www.cancercare.on.ca>)

PEBC Breast Cancer DSG page at:

<http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/>

Section 1: Clinical Practice Guideline

Section 2: Systematic Review

Section 3: Guideline Development and External Review - Methods and Results

### Question

In women with HER2/*neu*-overexpressing breast cancer:

1. Compared with adjuvant or neoadjuvant chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes (overall response rate, time-to-disease-progression, overall survival, toxicity, or quality of life)?
2. Compared with placebo or observation, does single-agent trastuzumab adjuvant or neoadjuvant therapy improve clinically meaningful outcomes?
3. What is the best way to identify women who will benefit from adjuvant or neoadjuvant trastuzumab therapy?
4. What are the adverse events associated with adjuvant or neoadjuvant trastuzumab therapy?
5. What are the optimal dose, schedule, and duration for adjuvant trastuzumab therapy?

### Recommendations and Key Evidence

**Trastuzumab should be offered for one year to all patients with HER2-positive node-positive or node-negative, tumour greater than 1 cm in size, and primary breast cancer and who are receiving or have received (neo)adjuvant chemotherapy. Trastuzumab should be offered after chemotherapy.**

- In the Herceptin Adjuvant (HERA) trial (1), the addition of one-year trastuzumab following (neo)adjuvant chemotherapy was superior to observation after chemotherapy in terms of disease-free survival (DFS) (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.43 to 0.67), recurrence-free survival (HR 0.50, 95% CI 0.40 to 0.63), and distant-disease-free survival (HR 0.40, 95% CI 0.40 to 0.66).
- In a combined analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial and the North Central Cancer Treatment Group (NCCTG) N9831 trial (2), the addition of one-year trastuzumab concurrent with adjuvant paclitaxel following adjuvant doxorubicin and cyclophosphamide was superior to no trastuzumab in terms of DFS (HR 0.48, p-value  $3 \times 10^{-12}$ ), time-to-first-distant-recurrence (TTR) (HR 0.47, p-value  $8 \times 10^{-10}$ ), and overall survival (OS) (HR 0.67, p-value 0.015).

### Qualifying Statements

- HER2 positive means the patient's breast cancer overexpresses HER2/*neu* (>10% cells positive with strong intensity staining) as determined by immunohistochemistry (IHC) or the HER2/*neu* gene is amplified as determined by fluorescent in situ hybridization (FISH).
- There is evidence in favour of both concurrent and sequential administration of trastuzumab with adjuvant paclitaxel or docetaxel (2,3) after three-weekly doxorubicin and cyclophosphamide. Therefore, it is the expert opinion of the Breast Cancer Disease Site Group (DSG) that, for patients receiving three-weekly doxorubicin and cyclophosphamide followed by paclitaxel or docetaxel, it may be reasonable to give trastuzumab either with the taxane or after it. However, in the B-31 trial, there was a rate of 4.1% congestive heart failure for concurrent paclitaxel and trastuzumab following doxorubicin and cyclophosphamide (4).
- The HERA trial allowed any "approved" adjuvant chemotherapy regimen, with over 90% of patients receiving anthracycline- or anthracycline/taxane-based regimens. The trastuzumab was started after all other therapy except hormonal therapy.
- The HERA trial dose schedule of trastuzumab was three-weekly 6 mg/kg for one year, with an 8 mg/kg loading dose in the first cycle.
- There were significantly more grade 3/4 adverse events (7.9% versus [vs.] 4.4%) and serious events (7.0% vs. 4.7%) in the HERA trial in those receiving trastuzumab compared to those under observation. However, that toxicity is considered acceptable, given the increase in survival.
- The dose and schedule of doxorubicin and cyclophosphamide was the same for the B-31 and N9831 trials, four three-weekly cycles of 60 mg/m<sup>2</sup> doxorubicin and 600 mg/m<sup>2</sup> cyclophosphamide. The dose and schedule of trastuzumab was also the same, 4 mg/kg trastuzumab as a loading dose followed by 51 weekly cycles of 2 mg/kg trastuzumab.
- The B-31 and N9831 dose and schedule of paclitaxel following doxorubicin and cyclophosphamide differed between the two trials; B-31 patients received four three-weekly cycles of 175 mg/m<sup>2</sup> paclitaxel, while N9831 patients received 12 weekly cycles of 80 mg/m<sup>2</sup> paclitaxel.
- The HERA trial discontinued its control (observation) arm but continues with a one-year trastuzumab and a two-year trastuzumab arm. Until the results of that trial are available, the relative merits of one versus two years of trastuzumab are unknown.

- There is evidence from the BCIRG 006 trial (3) that suggests that the combination of docetaxel, carboplatin, and trastuzumab may be similarly effective to doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab, with reduced cardiac toxicity. However, to date the full details of this trial, particularly the direct comparison of these two regimens, have not been published. Until such time as these results are available, the Breast Cancer DSG cannot make any recommendation regarding the docetaxel, carboplatin, and trastuzumab regimen.
- There is evidence from the FinHer trial (5) that indicates that nine weeks of trastuzumab, given concurrently with either vinorelbine or docetaxel prior to cyclophosphamide, epirubicin and 5-fluorouracil is superior to the same regimen without trastuzumab. However, neither of the base regimens compared in this trial are commonly used; until such time as randomized trials comparing these regimens to standard trastuzumab containing regimens are reported, the Breast Cancer Disease Site Group cannot make any recommendation regarding their use.
- So far, the only data available are for trastuzumab in patients who have (neo)adjuvant chemotherapy. There are no data available as yet for trastuzumab in patients who have received other forms of (neo)adjuvant therapy.
- For related recommendations, clinicians are encouraged to review the clinical practice guidelines listed under Related Guidelines. Before the end of 2006, the Breast Cancer Disease Site Group plans to create a summary practice guideline covering all areas of adjuvant systemic therapy.

**NOTE:** An earlier version of this clinical practice guideline was released to Ontario hospitals in July 2005 as part of the Drug Quality Therapeutics Committee-Special Oncology Subcommittee (DQTC-SOS) funding process in Ontario. This version, along with the systematic review and methods and results document that make up this evidence-based series, replaces that document.

#### **Related Guidelines**

- PG 1-7: *Adjuvant Taxane Therapy for Early-stage Invasive Breast Cancer* - January 2006
- PG 1-8: *Adjuvant Systemic Therapy for Node-Negative Breast Cancer* - May 2003.
- PG 1-15: *The Role of Trastuzumab (Herceptin) in the Treatment of Women with HER2/neu-overexpressing Metastatic Breast Cancer* - November 2005.
- EBS 1-17: *The Role of HER2/neu Expression in Systemic Therapy for Women with Breast Cancer* - In development.
- PG 1-20: *The Role of Taxanes in Neoadjuvant Chemotherapy for Women with Non-metastatic Breast Cancer* - December 2004.

## EVIDENCE-BASED SERIES #1-24

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3. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Pawlicki M, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC>T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC>TH) with docetaxel, carboplatin, and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study [abstract]. *Breast Cancer Res Treat* 12-8-2005;94 Suppl 1:A1
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## Evidence-based Series 1-24: Section 2

# The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/*neu*-overexpressing Breast Cancer: A Systematic Review

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## QUESTIONS

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## INTRODUCTION

Since the early 70s, many studies have shown that adjuvant chemotherapy can reduce recurrence and prolong survival in women with breast cancer (1). While this chemotherapy has generally been given in the adjuvant setting (i.e., following primary surgery for breast cancer), there is evidence (2) that, whether such chemotherapy is given in the neoadjuvant setting (all or partly prior to primary breast surgery) or the classical post-surgery adjuvant setting (all following surgery), it is of equal efficacy.

The HER2/*neu* gene encodes a 185-kd transmembrane glycoprotein (p185<sup>HER2/*neu*</sup>) that is a member of a family of growth-factor receptors with intrinsic tyrosine kinase activity. HER2/*neu* is overexpressed in 25% to 30% of human breast cancers (3). Overexpression of p185<sup>HER2/*neu*</sup> in patients with primary breast cancer is associated with a number of adverse

prognostic factors, including advanced-stage axillary lymph node involvement, absence of estrogen and progesterone receptors, increased S-phase fraction, and high nuclear grade (4,5).

The murine monoclonal antibody against HER2/*neu*, 4D5, has anti-proliferative effects against HER2/*neu* overexpressing breast cancers in vitro and against breast cancer xenografts (6-8). However, due to their immunogenicity, the therapeutic use of murine antibodies is limited clinically (9). Consequently, one of the more effective antibodies, 4D5, was humanized, resulting in a human immunoglobulin IgG1 agent that retains murine sequences only in the complementarity-determining regions. That antibody became known as trastuzumab (Herceptin<sup>®</sup>) and was approved for the treatment of metastatic breast cancer in Canada in August 1999. Trastuzumab in combination with paclitaxel (10), doxorubicin plus cyclophosphamide (11), or docetaxel (12) has been shown to provide a significant advantage over chemotherapy alone in first-line therapy for metastatic breast cancer.

## **METHODS**

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by one member (YM) of the PEBC Breast Cancer Disease Site Group (BCDSG) and one methodologist (HM).

This systematic review is a convenient and up-to-date source of the best available evidence on adjuvant and neoadjuvant therapy with trastuzumab in women with HER2/*neu* overexpressing breast cancer. The body of evidence in this review is comprised primarily of mature randomized controlled trial data. That evidence forms the basis of the clinical practice guideline (Section 1 of this Evidence-based Series report) developed by the BCDSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### **Literature Search Strategy**

MEDLINE and EMBASE were searched up to the first week of May 2006 using the search criteria outlined in Table 1. The online abstract databases of the American Society of Clinical Oncology (ASCO) annual meetings (<http://www.asco.org>), San Antonio Breast Cancer Symposia (<http://www.sabcs.org>), and the European Society of Medical Oncology biennial congress (<http://www.esmo.org>), were all searched for appropriate data as shown in Table 2. The Cochrane Library was also searched for all entries that contained the keywords "trastuzumab" or "herceptin", with relevant items reviewed and included.

**Table 1. Search terms used for MEDLINE and EMBASE search.**

	<b>MEDLINE</b>	<b>EMBASE</b>
<b>Disease characteristics</b>	exp (breast neoplasms).ms [(breast or mammary).tw and (cancer or carcinoma or neoplasm).tw]	(breast cancer).et or [(breast or mammary).tw and (cancer or carcinoma or neoplasm).tw]
<b>Trial/publication characteristics</b>	(clinical trials, phase II).ms or (clinical trials, phase III).ms or (clinical trials, phase IV).ms or (controlled clinical trials).ms or (randomized controlled trials).ms or (meta-analysis).ms or (“review literature”).ms or (randomized controlled trial).pt or (controlled clinical trial).pt or (meta-analysis).pt, or review.pt or guideline.pt or (clinical trial, phase II).pt or (clinical trial, phase III).pt or (clinical trial, phase IV).pt or (clinical trial).pt	(phase 2 clinical trial).et or (phase 3 clinical trial).et or (phase 4 clinical trial).et or (randomized controlled trial).et or (“systematic review”).et or (practice guideline)/ or (meta-analysis).et
<b>Treatment characteristics</b>	(trastuzumab.kw or herceptin.kw) and (adjuvant.kw or neoadjuvant.kw)	(trastuzumab.kw or herceptin.kw) and (adjuvant.kw or neoadjuvant.kw)

Abbreviations: exp, “exploded” search term includes all subordinate search terms.

Codes: .et, Emtree subject term; .kw, abstract and title keyword; .ms, MeSH subject term; .pt, publication type keyword; .tw, title keyword.

**Table 2. Search methods used for meeting abstracts.**

<b>Meeting</b>	<b>Time Period Searched</b>	<b>Method</b>
American Society of Clinical Oncology (ASCO) annual meetings	1995 to 2005	All abstracts with the text “trastuzumab” or “herceptin” in abstract body, then found all titles with the text “adjuvant” or “primary”
San Antonio Breast Cancer Symposia	2002 to 2005	All abstracts with the keywords “trastuzumab” or “herceptin”, then found all titles with the text “adjuvant” or “primary”
European Society of Medical Oncology (ESMO) biennial congresses	2002, 2004	All abstracts with the keyword “trastuzumab”, then found all titles with the text “adjuvant” or “primary”

**Inclusion Criteria**

Trials were included if they met the following criteria:

- Trastuzumab, in combination or alone, was evaluated using a randomized controlled trial (RCT), meta-analysis, or evidence-based clinical practice guidelines.
- Reported outcomes included at least one of overall response rate, time-to-progression, overall survival, toxicity, or quality of life.
- Clinical trial results were published in full papers or publicly available abstracts and presentations.

**Exclusion Criteria**

Trials were excluded if they were published in a language other than English, as translation capabilities were not available.

**RESULTS**

**Literature Search Results**

Six randomized trials (13-21) were identified that met the inclusion criteria for this systematic review.

**Outcomes**

***Trastuzumab in the Adjuvant Setting***

To date, results have been published from five RCTs (13,14,16-18,22-24) . Those trials are summarized in Table 3.

**Table 3. Included adjuvant trastuzumab trials.**

Trial	Pts	Arms	Patient eligibility	HER2 method
HERA (13,14)	1693 1694 1694	CT CT → 1 yr H CT → 2 yr H	N+ or high risk N- (N0 but ≥T1c), resected invasive breast cancer	IHC 3+ or FISH+ (central)
NCCTG N9831 (16,17,25)	971 981 814	Arm A : AC → T Arm B : AC → T → H Arm C : AC → T + H	N+ or high risk (tumour > 1 cm if ER-, >2 cm if ER+) N-, resected invasive breast cancer	IHC 3+ or FISH+ (central)
NSABP B-31 (17,18)	872 864	Arm 1 : AC → T Arm 2 : AC → T + H	N+, resected invasive breast cancer	IHC 3+ or FISH+ (approved reference labs)
FinHer (26)	232	V + H → CEF → RT + TAM D + H → CEF → RT + TAM V → CEF → RT + TAM D → CEF → RT + TAM	N+, or (N-, Tum > 2 cm, and PgR-)	CISH+ (central)
BCIRG 006 (27)	3222	AC → D AC → D+H D+Pla+H	N+ or high risk N-	NR

Dosages:

HERA - H: 8 mg/kg q3wk x 1 → 6 mg/kg q3wk

N9831 - AC: 60/600 mg/m<sup>2</sup> q3wk x 4; T: 80 mg/m<sup>2</sup>/wk x 12; H: 4 mg/kg wk 1, 2 mg/kg/wk x 51

B-31 - AC: 60/600 mg/m<sup>2</sup> q3wk x 4; T: 175 mg/m<sup>2</sup> q3wk x 4; H: 4 mg/kg wk 1, 2 mg/kg/wk x 51

Finnish - CEF: 600/60/600 mg/m<sup>2</sup> q3wk x 3; V: 25 mg/m<sup>2</sup>/wk x 8; D: 100 mg/m<sup>2</sup> q3wk x 3; H: 2 mg/kg/wk x 9

BCIRG 006 – AC: 60/600 mg/m<sup>2</sup> q3wk x 4; D (in AC containing arms): 100 mg/m<sup>2</sup> q3wk x 4; H: q1wk during chemotherapy, q3wk during follow-up, dosage not reported; D+Pla: D 75 mg/m<sup>2</sup>, Pla AUC6, q3wk x 6.

Abbreviations: AC, doxorubicin plus cyclophosphamide ; BIG, Breast International Group; CEF, cyclophosphamide, epirubicin, and 5-fluorouracil; CISH, chromogenic in situ hybridization; cm, centimetre; CT, chemotherapy; D, docetaxel; FinHer, Finnish Herceptin; FISH, fluorescent in situ hybridization; H, trastuzumab; IHC, immunohistochemistry; N, node; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; PgR, progesterone receptor; Pla, carboplatin; RT, radiation therapy; T, paclitaxel ; TAM, tamoxifen; Tum, tumour; V, vinorelbine;

***HERA trial***

The results of a planned interim analysis of the Breast International Group (BIG) HERA phase III trial were reported in a scientific symposium slide presentation (13) at the 2005 ASCO annual meeting and were then published in a peer-reviewed journal with supplementary appendices (14). The results from the most recent publication are used where possible. There were no notable changes between the ASCO presentation and the peer-reviewed publication. The regimens, arms, number of patients, patient eligibility, and method of HER2/*neu* status identification are described in Table 3.

In all arms, patients were treated with four or more cycles of an “approved” adjuvant and/or neoadjuvant chemotherapy regimen, given pre- or postoperatively, with or without radiation therapy. Neither the mechanism of approval nor a list of approved regimens was presented in the slides. HERA patients also received a variety of adjuvant endocrine therapies. Patients were stratified by nodal status, type of adjuvant chemotherapy regimen, hormone receptor status, endocrine therapy, age, and region, prior to randomization. Random assignment to the trastuzumab arms was done within seven weeks of day one of the last chemotherapy cycle or six weeks from the end of the radiotherapy or definitive surgery, whichever was last. However, the report did not make clear whether random assignment equated to initiation of therapy; the delay between chemotherapy and trastuzumab in that trial was not stated.

The primary endpoint of the study was disease-free survival (DFS), while recurrence-free survival (RFS), distant-disease-free survival (DDFS), overall survival (OS), and the comparison of one versus two years of trastuzumab were secondary endpoints. The analysis described in the presentation was a planned interim efficacy analysis at 475 events, which was half of the final analysis goal of 951 events. The median follow-up at the time of the analysis was one year; therefore, only the observation and one-year trastuzumab arms were included in the analysis, for a total of 3,387 patients (13,14). Selected baseline characteristics of the patients enrolled in the trial are summarized in Table 4.

**Table 4. Selected baseline patient characteristics, HERA trial (13,14).**

	Observation (% of pts)	1 year H (% of pts)
<b>Node-negative</b>	32.9%	32.1%
<b>Adjuvant anthracycline chemotherapy, no taxane</b>	68.3%	67.9%
<b>Adjuvant anthracycline and taxane chemotherapy</b>	25.6%	26.0%
<b>Adjuvant endocrine therapy (of hormone receptor-positive patients)</b>	92.9%	89.9%
<b>Neoadjuvant therapy</b>	~10%	

Abbreviations: H, trastuzumab; pts, patients.

The efficacy results of the HERA trial are summarized in Table 5. That trial found a significant advantage to treatment with one year of trastuzumab after chemotherapy over observation in terms of DFS, RFS, and DDFS but not OS. The presentation states that the clinical benefits of trastuzumab over observation were “independent of patients’ baseline characteristics (nodal status, hormone receptor status, etc.) and of type of adjuvant chemotherapy received.” The toxicity and adverse event results are summarized in Table 6.

**Table 5. Efficacy results, HERA trial (13,14).**

Comparison	Efficacy Measure	Number of Events	HR (95% CI)	Log Rank p-value
1 yr H vs Obs	DFS	127 vs. 220	0.54 (0.43 to 0.67)	<0.0001
	RFS	113 vs. 209	0.50 (0.40 to 0.63)	<0.0001
	DDFS	98 vs. 179	0.40 (0.40 to 0.66)	<0.0001
	OS	29 vs. 37	0.76 (0.47 to 1.23)	0.26

Abbreviations: CI, confidence interval; DDFS, distant-disease-free survival; DFS, disease-free survival; H, trastuzumab; HR, hazard ratio; Obs, observation; OS, overall survival; RFS, recurrence-free survival; vs, versus; yr, year.

**Table 6. Toxicity and adverse events, HERA trial (13,14).**

	Observation (% of pts)	1 year H (% of pts)	Comparison p-value
<b>At least one grade 3/4 adverse event</b>	<b>4.4%</b>	<b>7.9%</b>	<b>&lt;0.001</b>
<b>At least one serious adverse event</b>	<b>4.7%</b>	<b>7.0%</b>	<b>0.007</b>
<b>Fatal adverse events</b>	0.2%	0.4%	0.34
<b>Withdrawal from treatment due to safety</b>	NA	8.5%	NA
<b>Decrease by ≥10 EF points and LVEF &lt;50%</b>	<b>2.2%</b>	<b>7.1%</b>	<b>&lt;0.001</b>
<b>Cardiac death</b>	0.1%	0%	1

Comparisons in bold are statistically significant.

Abbreviations: EF, ejection fraction; LVEF, left ventricular ejection fraction; pts, patients.

Based on the interim analysis, patients on the observation arm of the HERA trial are now being offered trastuzumab. It is not clear from the presentation whether that decision was made based on pre-planned criteria. The trial is still ongoing in order to evaluate the efficacy and toxicity of the two trastuzumab schedules, one year versus two years.

*North Central Cancer Treatment Group (NCCTG) N9831 Trial*

Preliminary results from the NCCTG N9831 phase III trial were reported in slide presentation form during a scientific symposium at the 2005 ASCO annual meeting (16). In addition, cardiac safety data from that trial was reported in abstract form at the same meeting (28). A previous report on the same trial (29) was identified, but that report did not provide trastuzumab-specific data. More recently, additional data from the trial was part of a report on the combined analysis of that trial and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial, described below (17). The most recent results are used where possible. The regimens, arms, number of patients, patient eligibility, and method of HER2/*neu* status identification are described in Table 3. The clinical endpoints of the trial were DFS and OS.

The trial involved three arms, as described in Table 3. In the doxorubicin plus cyclophosphamide (AC) → paclitaxel (T) → trastuzumab (H) arm (Arm B), the trastuzumab followed the paclitaxel, but the allowed interval between the end of chemotherapy and the start of trastuzumab, if any, was not stated. In the AC → T + H arm (Arm C), the first twelve weeks of trastuzumab therapy was concurrent with the paclitaxel cycles. Therefore, in both trastuzumab arms, all patients received 52 weekly cycles of trastuzumab; the only difference was the timing in relation to the paclitaxel cycles. After the paclitaxel cycles were completed, radiation and/or hormonal therapy were used as indicated.

The results reported at the 2005 ASCO meeting were the consequence of an unplanned interim analysis done in response to the findings of the NSABP B-31 trial, described below (18). Therefore, the number of events at the time of that analysis did not meet the final analysis targets set in the trial design, and the results must be interpreted in that context. At the time of the interim analysis, the median follow-up was 1.5 years (16). The reported results of the trial are summarized in Table 5. The interim analysis found a significant advantage in terms of DFS, but not OS, for the use of H used concurrently with T after AC (Arm C), as opposed to H after T (Arm B). No significant association was found in terms of DFS or OS for the comparison of Arm A (no H) versus Arm B (H after chemotherapy). These results are presented in Table 7.

**Table 7. Disease-free and overall survival, NCCTG N9831 trial, interim analysis.**

Comparison	Efficacy Measure	Number of events	HR (95% CI) <sup>A</sup>	Log Rank p-value <sup>A</sup>
Arm B: AC → T → H vs Arm A: AC → T (16)	DFS	220	0.87 (0.67 to 1.13)	0.2936
	OS	79	0.85 (0.55 to 1.13)	0.4752
Arm C: AC → T + H vs Arm B: AC → T → H (16)	DFS	137	0.64 (0.46 to 0.91)	0.0114
	OS	56	0.74 (0.43 to 1.26)	0.2696
Arm C: AC → T + H vs. Arm A: AC → T (17)	DFS	140	0.55	0.0004

Hazard ratios are stated so that values of less than one favour the first listed arm.

<sup>A</sup> The analysis was stratified by nodal status and receptor status.

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NCCTG, North Central Cancer Treatment Group; OS, overall survival; vs, versus.

A separate abstract was published describing an interim cardiac safety analysis comparing Arm A (no trastuzumab) with Arm B (trastuzumab after paclitaxel) from that trial (30). The analysis had as its primary endpoint the proportion of cardiovascular events (congestive heart failure [CHF] and definite or probable cardiac death). The trial had pre-designated that a difference of 4% in the proportion of cardiovascular events would trigger suspension or closure of the trial. In the interim analysis, there were no cardiovascular events in Arm A and 13 events (2.2%, 95% CI 1.2% to 3.8%) in Arm B. (31) The presentation (16) reported the proportion of cardiovascular events for Arm C (concurrent trastuzumab) as 3.3% (95% CI 2.0% to 5.1%). No toxicity data beyond cardiac toxicity was reported. That trial is still ongoing, with pre-specified interim analyses planned at 50%, 67%, and 75% of the total planned events.

*NSABP B-31 trial and combined analysis with NCCTG N9831*

Results of the NSABP B-31 phase III trial were reported at a scientific symposium at the 2005 ASCO annual meeting (18). That report also included the results of a combined analysis of the data from both the B-31 trial and the NCCTG N9831 trial, referred to henceforward as the combined analysis. More recently, the results of the combined analysis have been reported in a peer-reviewed publication (17). There were no notable changes between the ASCO presentation and the peer-reviewed publication. The regimens, arms, number of patients, patient eligibility, and method of HER2/*neu* status identification are described in Table 3.

In the combined analysis, Arm 1 and Arm 2 of the B-31 trial were combined with Arms A and C of the N9831 trial, respectively. The primary endpoint of the trial was DFS, with OS and TTR as secondary endpoints. The results presented at the 2005 ASCO annual meeting (18) and in the publication (17) were the results of a pre-planned interim analysis to be done when half the planned final analysis total of 710 DFS events were reached. The median follow-up for the B-31 trial was 2.4 years, and the median follow-up for all patients included in the combined analysis was 2.0 years.

The efficacy results of the B-31 trial and the combined analysis are summarized in Table 8. The combined analysis found a significant advantage to the addition of H to chemotherapy in terms of all endpoints (18). Only DFS results were reported separately for the B-31 trial; those results also showed a significant advantage for the addition of trastuzumab to chemotherapy.

**Table 8. Disease-free survival, overall survival and time-to-first-distant-recurrence, NSABP B-31 trial and combined analysis of B-31 and NCCTG N9831 (17,18).**

Analysis	Comparison	Efficacy Measure	Num. of Events	HR	Log rank p-value
Combined	Arms 2/C: AC → T + H vs. Arms 1/A: AC → T	DFS	261 vs. 133	0.48	<0.0001
		TTR	193 vs. 96	0.47	<0.0001
		OS	92 vs. 62	0.67	0.015
B-31	Arm 2: AC → T + H vs. Arm 1: AC → T	DFS	171 vs. 83	0.45	<0.0001

Hazard ratios are stated so that values of less than one favour the first listed arm.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; Num., number; OS, overall survival; TTR, time-to-first-distant-recurrence; vs, versus.

Additional cardiac safety data were reported in a separate article (32). An incidence of 4.1% of cardiac events (31 CHF, no cardiac deaths) at three years in Arm 2, and an incidence of 0.8% (three CHF, one cardiac death) at three years in Arm 1 were reported. No toxicity data beyond cardiac toxicity was reported.

The B-31 trial was designed to be halted at the interim analysis if the disease-free survival advantage to one arm in the trial was significant at the p=0.0005 level. Based on the results described above, patient accrual for this trial has been halted, although patient follow-up is ongoing.

*Finnish Herceptin (FinHer) Trial*

A randomized trial was conducted in Finland that compared docetaxel to vinorelbine, followed by 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), with or without trastuzumab (33). Patients were eligible for inclusion if they had node-positive breast cancer, or node-negative, progesterone-receptor–negative breast cancer with a tumour size greater than two cm. 606 patients were randomized to receive either three three-weekly cycles of 100 mg/m<sup>2</sup> docetaxel or eight weekly cycles of 25 mg/m<sup>2</sup> vinorelbine. All patients then received three three-weekly cycles of 600 mg/m<sup>2</sup> cyclophosphamide, 60 mg/m<sup>2</sup> epirubicin, and 600 mg/m<sup>2</sup> 5-fluorouracil, followed by radiation therapy and, if estrogen-receptor positive, five years of tamoxifen. Patients whose cancers were chromogenic *in-situ* hybridization (CISH) confirmed HER2/*neu* positive were also randomized to nine weekly cycles of two milligrams/kilogram (mg/kg) trastuzumab, with a starting dose of four mg/kg, concomitantly with the vinorelbine or docetaxel cycles. Two-hundred and thirty-two CISH-confirmed patients were included in the reported analysis with a mean follow-up in the study was 36 months (34).

In this trial, patients treated with trastuzumab experienced better recurrence-free survival (RFS), the primary outcome, than those not treated with trastuzumab (Hazard ratio (HR) 0.42, 95% CI 0.21 to 0.83,  $p=0.01$ ). This increase in RFS was independent of the type of chemotherapy received (docetaxel or vinorelbine). Patients treated with trastuzumab also experienced fewer distant recurrences (HR 0.29, 95% CI 0.13 to 0.64,  $p=0.002$ ). There was no statistically significant difference in survival (HR 0.41, 95% CI 0.16 to 1.08,  $p=0.07$ ).

In addition to efficacy measures, adverse events and cardiac toxicity data were reported. Left ventricular ejection fraction (LVEF) was measured by ultrasound or isotope cardiography at four points: prior to the first cycle of chemotherapy, at the last chemotherapy cycle, twelve months after the last cycle, and thirty-six months after the last cycle. Using an ANCOVA model, the difference in LVEF was not found to be statistically significantly different at twelve months (1.7% absolute increase in trastuzumab-treated patients, 95% CI -0.1% to 3.5%,  $p=0.06$ ) but was significantly increased in patients treated with trastuzumab at 36 months (3.0% absolute increase, 95% CI 0.7% to 5.4%,  $p=0.01$ ). Therapy with trastuzumab was not associated with an increase in any of the adverse events measured.

*Breast Cancer International Research Group (BCIRG) 006 Trial*

A planned interim analysis of the BCIRG 006 was reported in abstract form at the 2005 SABCS (35). Patients were eligible for inclusion if they had node-positive or high-risk node-negative breast cancer. The primary end-point was DFS, with OS and safety as secondary end-points. The median follow-up was 23 months.

In the interim analysis, patients in both the AC→Docetaxel (D) plus trastuzumab arm (HR 0.49,  $p<0.00001$ ) and the docetaxel, carboplatin, and trastuzumab arm (HR 0.61,  $p=0.00015$ ) experienced better DFS than those in the AC→D arm. No statistically significant difference in DFS was measured between the two trastuzumab containing arms. There were significantly more symptomatic cardiac events in the AC→D plus trastuzumab arm over the AC→D arm (2.3% vs. 1.2%,  $p=0.046$ ) but not in the docetaxel plus carboplatin arm (1.2% vs. 1.2%,  $p=1.00$ ). Also, absolute LVEF decline of greater than 15% and below lower limit of normal was more common in the AC→D plus trastuzumab arm (2.4%) over both the AC→D arm (0.6%,  $p=0.001$ ) and the docetaxel plus carboplatin arm (0.4%,  $p=0.54$  for comparison with AC→D).

*Synthesizing the Evidence*

Because the number of trials with appropriate efficacy measures (DFS, OS, etc.) was small, and two of those trials have already been analysed in a combined analysis, no pooling of the evidence of the trials was performed.

### **Trastuzumab in the Neoadjuvant Setting**

The HERA trial, described above, included patients who received neoadjuvant chemotherapy. One additional RCT of trastuzumab in the neoadjuvant setting was identified. The trial reported by Buzdar et al (19) was a randomized phase II trial that compared paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), with the same chemotherapy combined with trastuzumab. It was originally intended to accrue 164 patients. However, based on the high pathological complete response (pCR) in the trastuzumab arm of the study, the trial was halted after 42 patients were enrolled. The report indicated that the decision to halt the trial was based on the results of the trial at that point and a conclusion by the trials Data Monitoring Committee, based on a Bayesian probability analysis, that continuing the trial to full accrual would not change the outcome; it was not based on a preplanned stopping rule. The efficacy and toxicity results of that trial are summarized in Table 9. The trial found a significant advantage in terms of pCR in patients treated with H plus chemotherapy versus those not treated with trastuzumab. The trial found no differences, in terms of cardiac safety, between the arms but found higher rates of neutropenia in the trastuzumab arm. An update on this trial was published in abstract form at the 2005 SABCS (36), which provided information on some additional non-randomized patients, and indicated that patients in the original study remained “free of disease without any clinical cardiac dysfunction”.

**Table 9. Efficacy results, trastuzumab in neoadjuvant chemotherapy.**

<b>Trial</b>	<b>Arms</b>	<b>cCR</b>	<b>cOR</b>	<b>pCR</b>	<b>G 3/4 Neutropenia</b>	<b>Febrile Neutropenia</b>
Buzdar et al (19)	CT alone	47%	95%	26% <sup>A</sup>	58%	42%
	CT plus H	91%	96%	65% <sup>A</sup>	91%	35%

<sup>A</sup> Significantly different, p=0.016.

Abbreviations : cCR, clinical complete response rate ; cOR, clinical overall response rate; CT, chemotherapy; H, trastuzumab; OR, overall response rate; pCR, pathological complete response rate; pOR, pathological overall response rate.

## **DISCUSSION**

### **1. Compared with adjuvant or neoadjuvant chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes (overall response rate, time-to-disease-progression, overall survival, toxicity, or quality of life)?**

Based on preliminary reports of three large RCTs, the addition of one year of trastuzumab, following a variety of adjuvant or neoadjuvant chemotherapy regimens, significantly improved the primary endpoint of DFS in patients with HER2/neu positive early breast cancer. Secondary endpoints of RFS, DDFS, and TTR in all studies, and OS in one combined study, were also significantly improved with the addition of trastuzumab. Those results are only applicable to women with HER2/neu overexpressing breast cancer who complete a minimum of four cycles of adjuvant or neoadjuvant chemotherapy. Although the majority of the patients in those studies had node-positive breast cancer, women with high-risk node-negative breast cancer were also included in HERA (32% were N0 but had tumours  $\geq$ T1c) and NCCTG 9831 (11% were N0 but had tumours >1cm if ER negative, >2cm if ER positive). Therefore,, those results are also generalizable to women with node-negative breast cancer meeting these criteria.

### **2. Compared with placebo or observation, does single-agent trastuzumab adjuvant or neoadjuvant therapy improve clinically meaningful outcomes?**

No trials were identified that compared single-agent trastuzumab to placebo or observation.

### **3. What is the best way to identify women who will benefit from adjuvant or neoadjuvant trastuzumab therapy?**

HER2 status should be determined in women receiving adjuvant or neoadjuvant chemotherapy for node-positive and high-risk node-negative breast cancer. HER2/neu status can be determined by a number of methods. In the reported clinical trials, HER2 positivity was determined either by measuring protein overexpression using immunohistochemistry (>10% cells positive with strong intensity staining) or by detecting gene amplification using FISH or CISH. Adequate standardization of methodology and laboratory quality assurance is essential, and, in the reported studies, a central lab or approved reference laboratory was used. In Canada, a consensus statement of pathologists is available (37) that recommends testing using IHC with FISH on equivocal IHC specimens.

### **4. What are the adverse events associated with adjuvant or neoadjuvant trastuzumab therapy?**

Based on experience in the metastatic setting, the concurrent use of trastuzumab and anthracyclines has prohibitive cardiac toxicity (38). Based on the current reports, the cardiac toxicity with adjuvant trastuzumab appears to be acceptable, although the reported rate of cardiac events was higher in the concurrent versus sequential trastuzumab arm (in NSABP B31 4.1% vs 0.7%, HR of 7.2; in NCCTG 9831 3.3% vs 2.2%). The non-cardiac toxicity reported appears acceptable.

### **5. What are the optimal dose, schedule, and duration for adjuvant trastuzumab therapy?**

In those studies, trastuzumab was administered in several doses and schedules: 1) in HERA trastuzumab was initiated after completion of one of various chemotherapy regimens, at a loading dose of 8 mg/kg followed by 6 mg/kg at 21-day intervals, for one or two years; 2) in NSABP B31 and NCCTG 9831, trastuzumab was initiated after AC chemotherapy, beginning concurrently with weekly or every-three-week (q 3 weekly) paclitaxel or, immediately following completion of weekly paclitaxel, at a loading dose of 4 mg/kg followed by 2 mg/kg weekly, for one year; 3) in the Finish trial, trastuzumab was initiated concurrently with either docetaxel or vinorelbine, at a loading dose of 4 mg/kg followed by 2 mg/kg weekly for nine weeks. None of those adjuvant trastuzumab dose schedules have been directly compared, but, in metastatic breast cancer, the q 3 weekly schedule is considered equivalent to the weekly schedule (39,40). The optimal timing of trastuzumab in relation to chemotherapy is not known. In the HERA trial publication, the allowed delay between the end of chemotherapy and the initiation of trastuzumab was not stated. In the combined analysis of NSABP B31/NCCTG9831, trastuzumab was given either concurrently with paclitaxel or after paclitaxel, also with the allowed delay not stated. The reported comparison of concurrent versus sequential trastuzumab is that of an unplanned interim analysis and must be interpreted with caution, particularly in light of the observed higher cardiac event rate with concurrent trastuzumab. The optimal duration of adjuvant trastuzumab is unknown. Only HERA was designed to address this question (one vs. two years), and that analysis is still pending.

#### **Related Recommendations**

There are currently several other documents that provide recommendations regarding adjuvant systemic therapy or therapy with trastuzumab, as shown in the Other Related Guidelines section at the end of this document. Clinicians are encouraged to review these recommendations in addition to those that make up this evidence-based series.

## ONGOING AND UNPUBLISHED TRIALS

The NCCTG N9831 trial (16,41) described above is still ongoing. The HERA trial (13) is also ongoing, although all patients on the observation arm are now being offered trastuzumab as described above. Patient accrual for the NSABP B-31 trial (13) was halted based on preplanned stopping rules, but patient follow-up is ongoing. Also, the final analysis of the BCIRG 006 trial has not yet been reported (42). In addition to those trials, there are a number of other ongoing RCTs, summarized in Table 10.

**Table 10. Ongoing RCTs of trastuzumab in the adjuvant or neoadjuvant setting.**

Trial Designation	Type of Trial	Setting	Arms	Target Accrual	Status
E-2198 (43)	Randomized Phase II	Adjuvant	T+H → AC T+H → AC → H <sub>1 yr</sub>	200	Closed
FRE-FNCLCC-PACS-04/005 (44)	Phase III	Adjuvant	See note <sup>A</sup>	2600 <sup>A</sup>	Closed
CLB-49808 (45)	Phase III	Neoadjuvant	See note <sup>B</sup>	396	Completed
UCLA-9911084 (46)	Phase III	Neoadjuvant	D+Carbo D+Carbo+H	75	Active

<sup>A</sup> Patients undergo two randomizations: FEC versus ED followed (for those HER2+) by H for 1 yr versus obs. Target accrual includes HER2- and HER2+ patients.

<sup>B</sup> Patients undergo three randomizations: neoadjuvant AC versus AC+Z, followed by neoadjuvant T versus T+H, followed by adjuvant H or obs, for a total of eight arms.

Abbreviations: AC, doxorubicin plus cyclophosphamide; Carbo, carboplatin; ED, epirubicin plus docetaxel; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; Pla, either carboplatin or cisplatin; T, paclitaxel; yr, year; Z, dexrazoxane.

## CONCLUSIONS

The benefit of adjuvant chemotherapy for breast cancer was established more than 30 years ago and, since then, subsequent generations of clinical trials have demonstrated an added benefit from superior chemotherapy regimens and comparable efficacy for chemotherapy given pre- or postoperatively (1). The cumulative effects of adjuvant chemotherapy, together with screening mammography, have contributed to the reduction in breast cancer mortality witnessed over the last decade (47). More remarkably, however, the magnitude of incremental benefit conveyed by adjuvant trastuzumab well exceeds the gains accrued by over three decades of adjuvant chemotherapy use. Adjuvant trastuzumab therapy should be offered to all women with HER2-positive breast cancer who complete adjuvant or neoadjuvant chemotherapy for node-positive or high-risk node-negative breast cancer.

## CONFLICT OF INTEREST

Three lead authors of this document (YM, DM, HM) reported no potential conflict of interest. KP reported receiving consultant or advisory fees from several pharmaceutical companies that produce agents evaluated by this document. MT reported receiving support through the National Cancer Institute of Canada for a clinical trial of trastuzumab from an involved pharmaceutical company.

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For a complete list of the Breast Cancer Disease Site Group, please visit the CCO Web site at <http://www.cancercare.on.ca/>

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### **Evidence-based Series 1-24: Section 3**

## **The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/*neu*-overexpressing Breast Cancer: Guideline Development and External Review - Methods and Results**

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A Quality Initiative of the  
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

**Report Date: May 12, 2006**

### **THE PROGRAM IN EVIDENCE-BASED CARE**

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

### **The Evidence-based Series**

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

## **DEVELOPMENT OF THIS EVIDENCE-BASED SERIES**

### **Development and Internal Review**

This evidence-based series was developed by the Breast Cancer Disease Site Group (BCDSG) of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the role of trastuzumab in (neo)adjuvant systemic therapy in women with HER2/*neu* overexpressing breast cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

### **Report Approval Panel Review**

Prior to the submission of this Evidence-based Series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel, and the response to them, are described below:

- *The panel expressed some concern that there was considerable overlap between this document and other documents either in development or currently available. A synthesis of these recommendations was requested.*

The authors and the BCDSG members agreed with the panel that a synthesis of all available adjuvant systemic therapy recommendations is necessary. The BCDSG is planning to create a synthesis document before the end of 2006 that should address these concerns. However, a complete synthesis of all of these recommendations is not possible within this document. A comment to this effect, and guidance to the reader regarding other available guidelines, was added to the Qualifying Statements of the Recommendations and to the Discussion in Section 2: The Systematic Review.

- *The panel was interested in whether additional data were available on the long-term toxicity of trastuzumab, as the follow-up period on the included studies is still fairly short. In addition, further discussion of the acceptability of the higher rate adverse events that occurred with trastuzumab was also requested.*

A definitive statement regarding the higher, but acceptable, rate of adverse events was added to the qualifying statements. Unfortunately, there are no currently available trials that address the long-term toxicity of trastuzumab in a setting comparable to the adjuvant setting.

- *The panel requested a comment that the recommendations had previously been released in an abridged form as part of the Ontario drug funding process.*

A statement regarding the earlier release of the clinical practice guideline was added to Section 1 of this document.

### **External Review by Ontario Clinicians**

Following the review and approval of the report by the PEBC Report Approval Panel, the Breast Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

<p><b>BOX 1: DRAFT RECOMMENDATIONS (sent for external review April 10, 2006)</b></p>
<p><i>Target Population</i> Women with HER2/neu-overexpressing breast cancer.</p>
<p><i>Recommendation</i> <b>Trastuzumab should be offered for one year to all patients with HER2-positive node-positive or node-negative, tumour greater than 1 cm in size, and primary breast cancer and who are receiving or have received (neo)adjuvant chemotherapy. Trastuzumab should be offered after chemotherapy.</b></p>
<p><i>Key Evidence</i></p> <ul style="list-style-type: none"> <li>• In the Herceptin Adjuvant (HERA) trial (1), the addition of one-year trastuzumab following (neo)adjuvant chemotherapy was superior to observation after chemotherapy in terms of disease-free survival (DFS) (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.43 to 0.67), recurrence-free survival (HR 0.50, 95% CI 0.40 to 0.63), and distant-disease-free survival (HR 0.40, 95% CI 0.40 to 0.66).</li> <li>• In a combined analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial and the North Central Cancer Treatment Group (NCCTG) N9831 trial (2), the addition of one-year trastuzumab concurrent with adjuvant paclitaxel following adjuvant doxorubicin and cyclophosphamide was superior to no trastuzumab in terms of DFS (HR 0.48, p-value <math>3 \times 10^{-12}</math>), time-to-first-distant-recurrence (TTR) (HR 0.47, p-value <math>8 \times 10^{-10}</math>), and overall survival (OS) (HR 0.67, p-value 0.015).</li> </ul>
<p><i>Qualifying Statements</i></p> <ul style="list-style-type: none"> <li>• HER2 positive means the patient's breast cancer overexpresses HER2/neu (&gt;10% cells positive with strong intensity staining) at the 3+ level as determined by immunohistochemistry (IHC) or the HER2/neu gene is amplified as determined by fluorescent in situ hybridization (FISH).</li> <li>• There is evidence in favour of both concurrent and sequential administration of trastuzumab with adjuvant paclitaxel after three-weekly doxorubicin and cyclophosphamide. Therefore, it is the expert opinion of the Breast Cancer Disease Site Group (DSG) that, for patients receiving three-weekly doxorubicin and cyclophosphamide followed by paclitaxel, it may be reasonable to give trastuzumab either with the paclitaxel or after it. However, in the B-31 trial, there was a rate of 4.1% congestive heart failure.</li> <li>• The HERA trial allowed any "approved" adjuvant chemotherapy regimen, with over 90% of patients receiving anthracycline- or anthracycline/taxane-based regimens. The trastuzumab was started after all other therapy except hormonal therapy.</li> <li>• The HERA trial dose schedule of trastuzumab was three-weekly 6 mg/kg for one year, with an 8 mg/kg loading dose in the first cycle.</li> <li>• There were significantly more grade 3/4 adverse events (7.9% versus [vs.] 4.4%) and serious events (7.0% vs. 4.7%) in the HERA trial in those receiving trastuzumab compared to those under observation. However, that toxicity is considered acceptable, given the increase in survival.</li> <li>• The dose and schedule of doxorubicin and cyclophosphamide was the same for the B-31 and N9831 trials, four three-weekly cycles of 60 mg/m<sup>2</sup> doxorubicin and 600 mg/m<sup>2</sup> cyclophosphamide. The dose and schedule of trastuzumab was also the same, 4 mg/kg trastuzumab as a loading dose followed by 51 weekly cycles of 2 mg/kg trastuzumab.</li> <li>• The B-31 and N9831 dose and schedule of paclitaxel following doxorubicin and cyclophosphamide differed between the two trials; B-31 patients received four three-weekly cycles of 175 mg/m<sup>2</sup> paclitaxel, while N9831 patients received 12</li> </ul>

- weekly cycles of 80 mg/m<sup>2</sup> paclitaxel.
- The HERA trial discontinued its control (observation) arm but continues with a one-year trastuzumab and a two-year trastuzumab arm. Until the results of that trial are available, the relative merits of one versus two years of trastuzumab are unknown.
  - So far, the only data available are regarding for trastuzumab in patients who have (neo)adjuvant chemotherapy. There are no data available as yet regarding for trastuzumab in patients who have received other forms of (neo)adjuvant therapy.
  - For related recommendations, clinicians are encouraged to review the clinical practice guidelines listed under in “Other Related Guidelines” section for related recommendations. Before the end of 2006, The Breast Cancer DSG plans to create a summary practice guideline covering all areas of adjuvant systemic therapy before the end of 2006.

**Methods**

Feedback was obtained through a mailed survey of 108 practitioners in Ontario (72 medical oncologists and 36 radiation oncologists or surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on April 10, 2008. Follow-up reminders were sent at two weeks (complete package mailed again). The BCDSG reviewed the results of the survey.

**Results**

Twenty-nine responses were received out of the 108 surveys sent (26.9% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, fourteen indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

**Table 1. Responses to eight items on the practitioner feedback survey.**

Item	Number (%) <sup>A</sup>		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a guideline, as stated in the “Introduction” section of the report, is clear.	100	0	0
There is a need for a guideline on this topic.	100	0	0
The literature search is relevant and complete.	85.7	14.3	0
The results of the trials described in the report are interpreted according to my understanding of the data.	100	0	0
The draft recommendations in the report are clear.	92.9	7.1	0
I agree with the draft recommendations as stated.	92.9	7.1	0
This report should be approved as a practice guideline.	100	0	0
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	92.9	7.1	0

<sup>A</sup> Out of 14 respondents.

**Summary of Written Comments and Response**

Four respondents (31%) provided written comments. The main points contained in the written comments, and the response of the BCDSG, with any actions taken, were:

1. *Concern was expressed regarding the role in the recommendation of concurrent trastuzumab with paclitaxel in the doxorubicin/cyclophosphamide followed by paclitaxel regimen. The respondent indicated that, while trastuzumab given concurrently with paclitaxel was found to be effective, the recommendation does not allow for concurrent therapy, even though the superiority of sequential or concurrent had not yet been established.*

The BCDSG believes that the second qualifying statement under the recommendation accurately describes the current state of the evidence and provides sufficient guidance to practitioners with regard to the use of concurrent trastuzumab.

2. *As the data regarding neoadjuvant trastuzumab was scant, a suggestion was made to remove the word “neoadjuvant” from the title of the guideline.*

Although the recommendation does not address the use of trastuzumab in the neoadjuvant setting, the BCDSG believes the current title of the document accurately describes its contents and should not be changed.

3. *New data was believed to be available by one respondent.*

All searches were updated to the first week of May 2006, and four additional references eligible for inclusion were identified (3-6). These references were added to Section 2; in addition, two new qualifying statements addressing two of the trials (3,4) were added, and an existing qualifying statement was modified, to account for this new evidence. The document authors did not believe these changes significant enough to require new RAP or external review.

4. *Concern was expressed by one respondent regarding the expense associated with trastuzumab therapy and whether the recommendation would be feasible to implement without further funding.*

The charge of the PEBC and the BCDSG is to develop practice guidelines based on the best scientific evidence available. The BCDSG does not address fiscal and policy issues in the context of an evidence-based series. However, as noted in the “Policy Review” section below, an earlier version of this guideline was submitted to the Drug Quality Therapeutics Committee-Special Oncology Subcommittee (DQTC-SOS) as part of a request for funding of adjuvant trastuzumab in the province of Ontario.

**POLICY REVIEW**

An earlier version of this clinical practice guideline was submitted in July 2005 to the DQTC-SOS as part of a request for the funding of trastuzumab for adjuvant systemic therapy for breast cancer.

**RELATED PRINT AND ELECTRONIC PUBLICATIONS**

Available at: <http://www.cancercare.on.ca/>:

- PG 1-7: *Adjuvant Taxane Therapy for Early-stage Invasive Breast Cancer* - January 2006.
- PG 1-8: *Adjuvant Systemic Therapy for Node-Negative Breast Cancer* - May 2003.
- PG 1-15: *The Role of Trastuzumab (Herceptin) in the Treatment of Women with HER2/neu-overexpressing Metastatic Breast Cancer* - November 2005.
- EBS 1-17: *The Role of HER2/neu Expression in Systemic Therapy for Women with Breast Cancer* - In development.
- PG 1-20: *The Role of Taxanes in Neoadjuvant Chemotherapy for Women with Non-metastatic Breast Cancer* - December 2004.

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